SERUM ALBUMIN BINDING ANTIBODIES FOR TUNEABLE HALF-LIFE EXTENSION OF BIOLOGICS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority of U.S. provisional patent application No. 62/661,871 filed on Apr. 24, 2018, the specification of which is hereby incorporated by reference in its entirety.

BACKGROUND

(a) Field

[0002] The subject matter disclosed generally relates to antibodies or antigen-binding fragments that bind to serum albumin. More specifically, the subject matter relates to antibodies or antigen-binding fragments that bind to serum albumin for half-life extension of biologics, as well as compounds, pharmaceutical compositions, nucleic acid vectors, cells comprising the nucleic acid vectors, and methods of removing molecules from serum.

(b) Related Prior Art

[0003] Biologics of less than 40-50 kDa in size possess short serum half-lives due to rapid renal clearance. Strategies to prolong the serum half-life of various biologics (antibody fragments, single-domain antibodies, enzymes, growth factors, peptides) are critically important for efficacy. The half-life of biologics can be extended through various techniques, including, but not limited to PEGylation, PASylation, conjugation to carbohydrates, fusion to an IgG Fc domain, fusion to serum albumin, and fusion to an albumin binding domain or antibody binding domain that recognizes serum albumin. In the latter case, single-domain antibodies (referred to as sdAbs, V_HHs, or nanobodies), which are naturally occurring autonomous binding domains found in Camelid species, are ideal agents for which to target serum albumin for half-life extension. The flexibility V_HHs offer in terms of modularity and functionality allow for fusion to many biologics, in both N- and C-terminal orientations, without compensating target binding affinities or specificity.

[0004] The requirements for V_HH-based half-life extension of biologics are as follows: (i) high affinity binding and species cross-reactivity of the V_HH to the relevant serum albumins (human, monkey, rat, mouse) at pH 7.4, (ii) high affinity binding and species cross-reactivity of the V_HH to the relevant serum albumins (human, monkey, rat, mouse) at pH 5.5, (iii) the anti-serum albumin V_HH cannot compete with FcRn for albumin binding, and (iv) the anti-serum albumin V_HH must retain functionality when fused to biologics through linkers.

[0005] On the other hand, many harmful molecules (e.g., protein-based bacterial toxin or venoms) need to be removed as quickly as possible from the body. Increasing their rate of removal will have therapeutic effects and prevent disease. To remove harmful molecules from circulation, a direct neutralizing agent (e.g., antibody) can be used to neutralize the harmful effects of the toxic molecules. Presently, direct neutralization of many toxins is not efficacious enough (the toxic substance is not removed quickly enough from serum) leaving significant room for improvement of therapeutic antibody efficacy.

[0006] Therefore, there is a need for additional V_HHs which target multiple serum albumin species, for the purpose of extending the serum half-life of biologics or removal of harmful molecules.

[0007] The following application describes the isolation, characterization, and in vivo testing of several llama-derived V_HHs which target multiple serum albumin species, for the purpose of extending the serum half-life of biologics or removal of harmful molecules.

SUMMARY

[0008] According to an embodiment, there is provided an antibody or an antigen-binding fragment that binds to serum albumin comprising three complementarity determining regions (CDR1, CDR2 and CDR3), wherein the CDR1, CDR2 and CDR3 comprise an amino acid sequence comprising:

1)

GFLLRSNTM, (SEQ ID NO: 1)

IRPSGLT, (SEQ ID NO: 2)
and

HTRPPFQRDS (SEQ ID NO: 3)
or

ATRPPFQRDS, (SEQ ID NO: 4)
respectively; or

2)

GRTFIAYAM, (SEQ ID NO: 5)

ITNFAGGTT, (SEQ ID NO: 6)
and

AADRSAQTMRQVRPVLPY, (SEQ ID NO: 7)
respectively; or

3)

GRTFDNYVM, (SEQ ID NO: 8)

ISGSGSIT, (SEQ ID NO: 9)
and

AAGSRRTYYREPKFYPS, (SEQ ID NO: 10)
respectively; or

4)

GSTFSSSSV, (SEQ ID NO: 11)

ITSGGST, (SEQ ID NO: 12)
and

NVAGRNWVPISRYSPGPY (SEQ ID NO: 13)
or

AVAGRNWVPISRYSPGPY, (SEQ ID NO: 14)
respectively; or